Advances in the Treatment of Hyperlipidemia

C. Michael White, Pharm.D., FCP, FCCP
Professor and Head, Pharmacy Practice, UCONN
Co-Director, HOPE Collaborative Group, UCONN/Hartford Hospital

Objectives for Lecture

• At the conclusion of the lecture, the successful learner will be able to:
  – Select the LDL goal given specific patient characteristics
  – Select the appropriate first and adjunctive therapies for patients with differing patient profiles
  – Identify the clinical trial and pharmaco-economic results that drove these guideline recommendations
  – Apply knowledge of drugs to construct adequate patient monitoring plans and mitigate adverse events

ASCVD = ACS, stable angina, arterial revascularization, stroke/TIA, PAD, aortic aneurysm

Major ASCVD Events

- Recent ACS (within the past 12 mo)
- History of MI (other than recent ACS event listed above)
- Persistently elevated LDL-C (LDL-C ≥100 mg/dL [≥2.6 mmol/L]) despite maximally tolerated statin therapy and ezetimibe
- History of ischemic stroke
- Symptomatic PAD (claudication with ABI <0.85, previous revascular/amputation)
- History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD event(s)
- Heterozygous familial hypercholesterolemia
- Hypertension
- CKD (eGFR 15-59 mL/min/1.73 m²)
- Current smoking
- History of congestive HF

Very High Risk = 2 or more Column A [or] 1 from Column A and Multiple From Column B

Grundy S. JACC 2018; https://doi.org/10.1016/j.jacc.2018.11.003

AHA/ACC Risk Calculator
http://my.americanheart.org/professional/StatementsGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp then click on web based risk calculator in upper right.
For High or Very High Risk

- Regardless of the LDL goal, should get a 50% reduction in LDL from baseline
  - For example, someone with an LDL of 100mg/dL before their MI should get at least a 50% reduction even though this reduction will give the patient an LDL of 50mg/dL

Grundy S. JACC 2018; https://doi.org/10.1016/j.jacc.2018.11.003

AHA/ACC 2018 Statin Guidance

<table>
<thead>
<tr>
<th>LDL &gt;190mg/dL</th>
<th>ASCVD 10-yr Risk &gt;7.5%</th>
<th>Diabetes</th>
<th>ASCVD 10 yr Risk &gt;7.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Intensity</td>
<td>Statins or Intolerant</td>
<td>Moderate Intensity</td>
<td>Statins</td>
</tr>
</tbody>
</table>

High Intensity
- Moderate Intensity

Lipid Lowering Drugs and Potencies

<table>
<thead>
<tr>
<th>Lipid Lowering Drugs and Potencies</th>
<th>Lipid Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid Apheresis</td>
<td>-50 to -60%</td>
</tr>
<tr>
<td>Statins</td>
<td>-35 to -58%</td>
</tr>
<tr>
<td>PCSK9 Inhibitors</td>
<td>-35 to -58%</td>
</tr>
<tr>
<td>Lomitapide</td>
<td>-30 to -40%</td>
</tr>
<tr>
<td>Mipomersen</td>
<td>-25%</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>-15 to -20%</td>
</tr>
<tr>
<td>BAS</td>
<td>-5 to -20%</td>
</tr>
<tr>
<td>Niacin</td>
<td>-15 to -20%</td>
</tr>
<tr>
<td>Fibric Acid Deriv</td>
<td>-30 to -60%</td>
</tr>
<tr>
<td>Omega-3 FAs</td>
<td>-5 to -10%</td>
</tr>
</tbody>
</table>

Natural Products With Evidence to Show Benefits in LDL and Triglyceride Lowering (Niacin and Omega-3 Not Included Due to FDA Indication)

<table>
<thead>
<tr>
<th>Natural Products for Cholesterol Reduction</th>
<th>Lipid Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red yeast rice</td>
<td>-35.0 mg/dL*</td>
</tr>
<tr>
<td>Soluble fiber</td>
<td>-10.2% to -10.0%</td>
</tr>
<tr>
<td>Squalane and Stanols</td>
<td>-12.2 mg/dL*</td>
</tr>
<tr>
<td>Ginseng</td>
<td>0.4 mg/dL*</td>
</tr>
<tr>
<td>Almonds</td>
<td>0.8 mg/dL*</td>
</tr>
<tr>
<td>Green tea extract</td>
<td>-5.3 mg/dL*</td>
</tr>
<tr>
<td>Garlic</td>
<td>0.23 mg/dL*</td>
</tr>
</tbody>
</table>

Guideline Approved Statins

<table>
<thead>
<tr>
<th>Guideline Approved Statins</th>
<th>High Intensity</th>
<th>Moderate Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL Reduction &gt;50%</td>
<td>Atorvastatin 40-80mg</td>
<td>Atorvastatin 10-20mg</td>
</tr>
<tr>
<td>LDL Reduction 30-50%</td>
<td>Rosuvastatin 20-40mg</td>
<td>Rosuvastatin 5-10mg</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>20-40mg</td>
<td>Simvastatin 20-40mg</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>40-80mg</td>
<td>Pravastatin 40-80mg</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>40mg</td>
<td>Lovastatin 40mg</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>2-4mg</td>
<td>Fluvastatin 40mg BID</td>
</tr>
</tbody>
</table>

Grundy S. JACC 2018; https://doi.org/10.1016/j.jacc.2018.11.003
Guideline Approved Adjuncts

<table>
<thead>
<tr>
<th>Reduction to Goal</th>
<th>Adjuncts</th>
<th>Cost/Year</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>20%</td>
<td>Ezetimibe + BAS PCSK9 Inh</td>
<td>++</td>
<td>Impossible to have cost/QALY &lt;$100,000/year</td>
</tr>
<tr>
<td>30%</td>
<td>Ezetimibe + BAS PCSK9 Inh</td>
<td>++</td>
<td>Effective, safe, well tolerated, low cost, proof of event reduction</td>
</tr>
<tr>
<td>40%</td>
<td>Ezetimibe + BAS PCSK9 Inh</td>
<td>+++</td>
<td>Effective, safe, well tolerated, proof of event reduction but very high cost</td>
</tr>
</tbody>
</table>


Landmark Clinical Trials
Research Drives Guidelines

Statin vs. Placebo:
Landmark Clinical Trials

- **Primary Prevention:** WOSCOPS, AFCAPS/TexCAPS, ASCOT-LLA, JUPITER
  - Prav, lova, atorva, rosuva reduce cardiac events
- **Secondary prevention:** CARE, LIPID, 4S, HPS, GREACE
  - Prav, simva, atorva reduce mortality and recurrent events


LDL-C Lowering With Statins: Reduced CHD Events

LDL-Cholesterol (mg/dL)


PROVE-IT: Final Health Outcomes

<table>
<thead>
<tr>
<th>Primary end point</th>
<th>Pravastatin 40 mg (n=1973)</th>
<th>Atorvastatin 80 mg (n=2034)</th>
<th>Relative risk reduction, %</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality, MI, UA, PCI, CABG, Stroke</td>
<td>26.3%</td>
<td>22.4%</td>
<td>16%</td>
<td>0.005</td>
</tr>
<tr>
<td>Secondary end points</td>
<td>All-cause mortality 3.2%</td>
<td>2.2%</td>
<td>28%</td>
<td>0.07</td>
</tr>
<tr>
<td>Resuscitization</td>
<td>18.3%</td>
<td>16.3%</td>
<td>14%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Adjunct Trials w/ Additional LDL Lowering

<table>
<thead>
<tr>
<th>Therapy</th>
<th>IMPROVE IT</th>
<th>ODYSSEY</th>
<th>FOURIER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezetimibe 10mg + Simvastatin 40mg vs. Placebo</td>
<td>11.1% vs. 9.3%, P=0.001</td>
<td>11.0% vs. 9.2%, P=0.001</td>
<td></td>
</tr>
<tr>
<td>Evolocumab 140mg Q2W or 225mg Q4W vs. Placebo</td>
<td>11.1% vs. 9.3%, P=0.001</td>
<td>11.0% vs. 9.2%, P=0.001</td>
<td></td>
</tr>
<tr>
<td>Alirocumab 75mg or 150mg Q2W vs. Placebo</td>
<td>11.1% vs. 9.3%, P=0.001</td>
<td>11.0% vs. 9.2%, P=0.001</td>
<td></td>
</tr>
</tbody>
</table>

Inclusion Criteria:
- Everyone needed to be on moderate to max statins
- Population: Pts < 10 days of ACS, Pts w/ Hx of MI, Stroke, PAD, Pts < 1y post ACS
- Follow-up: 6 y, 2 y, 4 y

LDL - Baseline:
- 94mg/dL
- E: 53; P: 70mg/dl
- -24%
- 94mg/dL
- E: 30; P: 92mg/dL
- -67%
- 93mg/dL
- A: 53.3; P: 101mg/dL
- -55%


LDL-CV Event Reduction Relationship

- Cholesterol Treatment Trialists (CTT) assessment of all major statin vs. placebo, statin vs. statin, and statin + adjunct ezetimibe or PCSK9 inhibitor vs. statin trial
- For every 39mg/dL reduction in LDL, the 5-year risk of cardiovascular events is reduced by 22%
  - Holds for LDL’s as low as 30mg/dL


Not Everyone Should have an LDL of 30mg/dL

- If 50 of 100 of people over 5 years will have an ASCVD event, reducing that risk by 50% prevents 25 events
- If 10 of 100 people over 5 years will have an ASCVD event, reducing it by 50% prevents 10 events
  - 1/ARR = NNT
  - NNT = number needed to treat to prevent one event


NNTs for Different Patients To Reduce one Cardiovascular Event


PCSK9 Cost Effectiveness

- In an analysis, the cost-effectiveness of the PCSK9 inhibitors was estimated
- If the NNT on PCSK9 inhibitor therapy is 30 to 50, 15 to 29, or 10 to 14, therapy would cost ~$300,000, ~$280,000, or ~$150,000 per quality adjusted life year (QALY) at $14,000 per year
  - Currently priced at $6,000, PCSK9 with an NNT of 30-50 would be reasonably cost effective (~$64,285 per QALY)

**Statin + HDL Increasing Adjunctive Therapy**

- Adjunctive therapies improve lipid effects over statins alone
- Therapy to raise HDL
  - Niacin + Simva vs. Simva alone (AIM-HIGH, HPS-THRIVE)
  - Fenofibrate + Statin vs. Statin alone (ACCORD)
  - CETP Inhibitors + Statin vs. Statin Alone (ILLUMINATE)
- Combo does not impact final cardiovascular health outcomes (death, MI, ACS, stroke, revascularization)
- These drugs had little to no LDL lowering and niacin trials had high withdrawal rates

**Specifics of Lipid Lowering Drugs**

**Drug Therapy: Statins**

- Contraindications
  - Pregnancy, breastfeeding (category X)
  - Active liver disease or high unexplained liver transaminases (AST, ALT, LDH)
- Fatty liver can raise liver transaminases and statins don’t worsen it (and may help treat it)
- LFTs checked at baseline and when clinically indicated
  - Normal: AST 0-35mg/dL, ALT 5-40mg/dL, LDH 50-150mg/dL
- No resolution of LFT elevation, liver biopsy
- Pravastatin, rosuvastatin, simvastatin has lower risk of LFT elevation/hepatotoxicity than atorvastatin
- Greater risk with concurrent fibrate or niacin use

**Proteinuria**

- Incidence 1.1% rosuvastatin vs. 0.4% other statins
- Excretion of α-1 & β-2 microglobulin, not albumin
- Reduced reabsorption of small proteins usually reabsorbed in kidney tubules
- If hematuria (blood in urine), halt statin therapy til resolved and switch to another statin or another class

**Muscle Toxicity**

- Myalgia
  - Muscle pain
  - IL-6, IL-1β, TNF, Type 2 diabetes, insulin resistance
- Rhabdomyolysis
  - Severe muscle weakness without myalgia preceding it
  - Can cause chronic renal failure, death
  - Myoglobinuria and myoglobinemia common
- Myoglobinemia and myoglobinuria common
- Brownish or black urine
- Can cause renal failure
- Can cause prolonged muscle weakness needing rehabilitation
- Greater risk of rhabdomyolysis with simvastatin and lovastatin than hydrophilic statins (atorvastatin, pravastatin, fluvastatin, pitavastatin)
- Greater risk with concurrent fibrates, daptomycin, colchicine, niacin or for simvastatin, lovastatin, atorvastatin the use of CYP3A4 inhibitors

**Persistent ALT > 3 × ULN Frequency by % LDL-C Reduction**

Ref: Prescribing Information and Summary Basis of Approval documents.

**NEW**

AHFS 2001, FDA NMAC Advisory Panel (7/13/00 from www.FDA.gov)
Metabolic Pathways & Rhabdomyolysis

• Lovastatin, simvastatin, and atorvastatin are CYP3A4 substrates
  – Inhibitors of CYP3A4 increase risk of rhabdomyolysis
    • Lower risk with atorvastatin
  – Lovastatin and simvastatin are contraindicated with potent CYP3A4 inhibitors &
  Lovastatin, simvastatin, and atorvastatin have maximum dosing limits with CYP3A4
  inhibitors (see PIs)
  – CYP3A4 inhibitors: Azole antifungals (ketoconazole, itraconazole),
    macrolides (erythromycin, clarithromycin, troleandomycin),
    cyclosporin, nefazodone, non-dihydropyridine CCBs (diltiazem,
    verapamil), protease inhibitors (saquinavir, indinavir, ritonavir,
    amprenavir), amiodarone, dronedarone
  – 93% of simvastatin/lovastatin rhabdomyolysis cases occur w/ concurrent
    CYP3A4 inhibitors

Diltiazem + Lovastatin
High Variability in Interaction Magnitude

Effect of Gemfibrozil on Statin Plasma Concentrations

Statin/Fibrate Combinations

Intra-Muscle IC50 for Synthesis

Why Muscle Toxicity?

Why Muscle Toxicity?

Drug PIs.
Effect of Gemfibrozil and Fenofibrate on Rosuvastatin Plasma Concentrations

<table>
<thead>
<tr>
<th>AUC ratio of Rosuvastatin</th>
<th>Gemfibrozil</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>0.4</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>0.6</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>0.8</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>1.0</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>1.2</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>1.4</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>1.6</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>1.8</td>
<td>1.07</td>
<td>1.07</td>
</tr>
<tr>
<td>2.0</td>
<td>1.07</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Pitavastatin

- Normal doses 1–4mg
- Substrate for Uridine Diphosphate Glucuronosyltransferase (UGT)
  - Piava contraindicated with cyclosporin
  - Max dose 2mg with rifampin
  - Max dose 1mg with erythromycin
- Atazanavir, lopinavir, ritonavir have minor interaction

Dosing Pearls: Absorption

- Bioavailability of lovastatin ↑ 50% by food
  - High fiber meals reduce bioavailability
  - Dose with dinner for most food with least fiber
- Can’t use lovastatin with bile acid sequestrants
  - Both need dosing with meals

Dosing Pearls: Half-Life

- Short half-life drugs (fluvastatin, pravastatin) should optimally be dosed QHS
  - This is because night is the optimal time for circadian activation of HMG CoA reductase
- Others can be dosed at any time
Final Exam On Guidelines

Conclusions

- LDL is bad cholesterol, increases ASCVD risk
- Given the NNT, there are individual LDL targets for people based on baseline risk
- Statins are first line therapy to achieve LDL goals
  - Maximize statin dose or switch between statins before leaving statin class or using adjunctive therapy
  - Ezetimibe and PCSK9 Inhibitors are the best studied adjuncts to statins if additional LDL is needed
  * Role of bile acid sequestrants reappraised for event reduction, niacin does not provide additional benefits

Conclusions

- Simva, lova, atorva are CYP3A4 substrates and pitava is a UGT substrate
  - Myriad of inhibitors that increase muscle risk
- Counsel on statin muscle symptoms and check CK when symptoms arise
  - Warnings if CK is >3X ULN, DC if >10X ULN
- Three statins have targeted ingestions times
  - Lova at dinner, prava and fluva at bedtime

Conclusions

- PCSK9 inhibitors are new, expensive, potent LDL reducers
- Ezetimibe is not as potent but cheaper than PCSK9s
- Each drug class has monitoring parameters and counseling points that should be communicated to patients
- Drug within a class have features that differentiate it from the others, knowing those features empowers you to be the drug expert

Questions?

Hypertriglyceridemia Therapy
Hypertriglyceridemia Risks

- Hypertriglyceridemia diagnosis made on fasting triglyceride levels only


Hypertriglyceridemia Risks

- Medications that can cause hypertriglyceridemia/pancreatitis: A TV FEAST PAPA, I ACT

<table>
<thead>
<tr>
<th>A</th>
<th>TV</th>
<th>FEAST</th>
<th>PAPA</th>
<th>I</th>
<th>ACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Furosamide</td>
<td>Pentamidine</td>
<td>Isoniazid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Enteroga</td>
<td>Aprotinin</td>
<td>Antithrombotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aprotinin Acid</td>
<td>Azathioprine</td>
<td>Progest</td>
<td>Clofibrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins (containing tubo lics)</td>
<td>Aspirinase</td>
<td>Antacids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazides</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Hypertriglyceridemia Therapy

- Diet and exercise to achieve weight reduction, limit simple carbohydrates (sugar, starch, beer, wine)
- Statins are first line if LDL goal not met and triglycerides <500mg/dL
- Fibrates are first-line therapy if triglycerides >500mg/dL
- Fibrates, niacin, or omega-3 fatty acids alone or in combination with statins are alternatives
- Statins are not monotherapy in patients with severe or very severe hypertriglyceridemia

Berglund L. J Clin Endocrinol Metab 2012; 97:2969.

AAFP Triglyceride Guidelines 2007

Omega-3 FAs

- Dosing
  - 2-4g for triglyceride reduction
- Main ADEs
  - Dyspepsia
  - Burping fish oil smell
  - Nausea
  - Diarrhea

ESC 2016: Lifestyle Modifications

- Lifestyle modifications to reduce % of total fat intake
- Increase dietary fiber
- Increase mono- or polyunsaturated fats
- Reduce saturated fats
- Reduce trans fats
- Reduce dietary cholesterol
- Reduce salt intake
- Control blood pressure
- Control blood glucose
- Control body weight
- Control alcohol intake
- Control physical activity
- Control smoking
- Control stress
- Control tobacco use
- Control sedentary behavior
- Control dietary habits
- Control sleep habits
- Control dietary intake
- Control dietary supplements
- Control dietary habits
- Control dietary intake
- Control dietary supplements